Prefilled polymer BFS droppers/dispensers

Comparator*: Single dose vial (liquid) and dropper/dispenser

Section 1: Summary of innovation

1.1 Example images:

PATH prototype of BFS oral squeeze tube in a five-dose strip

Image: provided by PATH

1.2. Description of innovation:

- Blow-fill-seal (BFS) is an aseptic filling process that is widely used to produce a variety of pharmaceuticals in polymer primary containers. In the blow-fill-seal process, a polymer resin is melted into a parison, which is blown into a mould, filled, and sealed, all in a continuous process within a single piece of equipment. This is in contrast to preformed polymer primary containers, in which the container is first produced and sterilized, and then shipped to a different site for filling and sealing.
- A wide variety of different container designs are feasible with BFS.
    - For oral or intranasal vaccines, BFS containers can be designed as squeeze tube dropper or dispenser devices for delivery of the container's contents directly to the mouth or nostrils. This approach is the focus of this Technical Note.
    - For single-dose parenteral vaccines, BFS containers can be used similar to glass ampoules, with the top twisted off and an AD N&S used to draw up and inject the vaccine. BFS containers can also be designed with inset septum, similar to a glass vial. These innovations are reviewed in the Parenteral BFS Primary Container Technical Note.
    - BFS has the potential to be used for production of compact prefilled autodisable devices (CPADs), which are reviewed in the CPAD Technical Note.

* For the existing vial presentations of liquid and lyophilised vaccines, single dose vials, rather than multi-dose vials (MDVs) were used for the comparator, because in most cases, the innovation being considered is a single-dose presentation. However, when multi-dose vials are currently used by countries and would be the true comparator for countries, a comparison against the multi-dose vial will also be conducted under Phase II if this innovation is prioritised and for antigens where multi-dose vials are used by countries.

- A BFS dropper produces metered-size droplets, and could be used for small dose volume vaccines such as oral polio vaccine (OPV), including multidose presentations. A BFS dispenser emits a stream of vaccine and could be used for vaccines such as rotavirus and cholera that typically have a larger dose volume.
- BFS can facilitate development of container designs that are optimized for efficient packing, including conjoined single-dose containers that stack or fold within a secondary carton. Labelling space and costs can be minimized if single-dose BFS containers are designed to be rendered open by separating them from a strip that holds the label and vaccine vial monitor (VVM) for multiple individual containers (a multi-mono-dose [MMD] configuration) (1).
- In 2019, GlaxoSmithKline's (GSK's) Rotarix oral rotavirus vaccine was the first vaccine to be WHO prequalified in a BFS container (2). The BFS presentation of Rotarix is in a 5-dose MMD strip and has a smaller cold chain volume per dose (11.8 cm^3) than the previous preformed squeeze tube presentation of Rotarix (17.1 cm^3).
- The BFS filling process exposes the container's contents to heat, and although methods exist to minimize temperature excursions during BFS filling, concerns have been raised about the compatibility of BFS with vaccines and other temperature-sensitive biologics. However, stability studies with a number of live and subunit liquid vaccines, including rotavirus, LAIV, respiratory syncytial virus (RSV), and pneumococcal conjugate vaccine (PCV), have demonstrated that the vaccine was not impacted by the BFS process (3,4).
- Depending on the vaccine, the container's design, and the intended storage conditions, some vaccines in BFS may require a foil overwrap to prevent gas and water vapour ingress/egress through the polymer.

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Rotarix BFS squeeze tubes  Image source: provided by GSK	**GSK** https://www.gsk.com/	In 2019, GSK licensed a new presentation of Rotarix vaccine in a strip of 5 single-dose squeeze tubes (2).

VIPS is a Vaccine Alliance project from Gavi, World Health Organization, Bill & Melinda Gates Foundation, PATH and UNICEF

Product name; Image	**Developer (place); website**	**Brief description, notes**
Stacked packaging configuration in secondary carton  Image source: provided by GSK		
BFS containers (various)  Image source: Rommelag	**Rommelag** https://www.rommelag.com/en/	Rommelag is a manufacturer of BFS equipment, and has developed a variety of different BFS squeeze tube, ampoule, and vial designs.

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- BFS containers have the potential to be more compact than single-dose glass vials and to reduce cold chain storage volumes.
- For vaccines delivered orally or intranasally, BFS containers can be used as a squeeze tube dropper or dispenser to deliver the dose, eliminating the need for a separate delivery device (1).

2.2 Key challenges:

- The space saved in the cold-chain will be dependent on container design, how much space is required for product labelling, and whether an overwrap is required (5).

2.3 Additional important information

- BFS primary containers can be less costly to produce than single-dose glass vials or preformed polymer droppers/dispensers (5).
- BFS eliminates issues of glass such as delamination and cracking (which results in production loss or recalls) or shattering during transport.
- Polymer containers such as BFS can be disposed of more easily by incineration than glass primary containers.
- Vaccine manufacturers must conduct stability studies and production validation to support regulatory approval of each vaccine that is switched to a BFS presentation.

VIPS is a Vaccine Alliance project from Gavi, World Health Organization, Bill & Melinda Gates Foundation, PATH and UNICEF

SECTION 3: Evaluation criteria

3.1 Health impact criteria

Indicator: Ability of the vaccine presentation to withstand heat exposure

*Legend: Green: **Better** than the comparator: The innovation includes features that may increase heat stability; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator: The innovation includes features that may decrease heat stability, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 2.

Ability of the vaccine presentation to withstand heat exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	BFS is a primary container technology and does not impact the temperature stability of the vaccine.

	***No difference** to the comparator*

Indicator: Ability of the vaccine presentation to withstand freeze exposure

*Legend: Green: **Better** than the comparator: The innovation includes features that may increase freeze resistance; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator: The innovation includes features that may decrease freeze resistance, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral	BFS is a primary container technology and does not impact the freeze resistance properties of the vaccine.

	***No difference** to the comparator*

3.2 Coverage and equity criteria

Indicator: Ease of use[a]

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 4.

Ease of use	Parameters to measure against a comparator	Score	Assessment
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation avoid reconstitution and is that an improvement?**	Neutral	BFS droppers/dispensers are only compatible with liquid vaccines.
	Does the innovation require fewer vaccine product components?	Better	For oral vaccines, BFS containers eliminate the need for a separate delivery device.
	[b]**Does the innovation require additional components or equipment (such as scanners or label readers)?**	NA	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	For an oral vaccine, preparation steps are reduced as there is no need for a separate delivery device (1).
	Does the innovation improve dose control?	Better	BFS droppers/dispensers are a prefilled device that deliver a metered dose directly to the mouth or nostrils and do not require drawing a dose into a separate delivery device. The innovation would thus potentially improve dose control compared to use of a single-dose vial.

[a] Ease of use can prevent missed opportunities resulting from the complexity of preparation and administration procedures. It could also impact the ability for lesser trained personnel to administer the vaccine (incl. self-administration). It can be assessed based on usability data from field studies (or based on design of innovation if field studies not available).

[b] This parameter is only assessed for RFID/barcodes, for all other innovations it is not applicable (N/A).

	Does the innovation improve targeting the right route of administration?	Better	For vaccines delivered orally, BFS squeeze tubes have the potential to reduce the risk of accidental injection by differentiating the vaccine from standard parenteral vaccine glass vial presentations (6).

	Better *than the comparator*

Indicator: Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities

*Legend: Green: **Better** than the comparator for one of the parameters; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator for one of the parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 5.

Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • *Assessment of the potential to reduce stock outs based on the innovation's features*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation require fewer components?	Better	For oral vaccines, BFS containers eliminate the need for a separate delivery device as the container can be used as a dispenser or dropper.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	The innovation does not include labelling that facilitates product tracking similar to the comparator.

	Better *than the comparator*

VIPS is a Vaccine Alliance project from Gavi, World Health Organization, Bill & Melinda Gates Foundation, PATH and UNICEF

Indicator: Acceptability of the vaccine presentation and schedule to patients/caregivers

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**; Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Painful or not painful	Neutral	A BFS container does not impact the recipient's experience of vaccine delivery.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	A BFS container does not impact the recipient's experience of vaccine delivery.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers		

	No difference *to the comparator*

3.3 Safety criteria

Indicator: Likelihood of contamination

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 7.

Likelihood of contamination	Parameters to measure against a comparator	Score	Assessment
• *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?**	Neutral	A BFS dispenser/dropper is intended for use with liquid vaccines only.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	For oral vaccines, BFS containers eliminate the need for a separate delivery device, reducing the likelihood of contamination occurring while assembling a dropper to the vial or filling a separate oral dispenser. However, oral vaccine devices are not required to be sterile, so overall risk to the patient is unchanged.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	For an oral vaccine, there is no need to draw a dose into a separate delivery device if packaged in a BFS container.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Better	Oral delivery devices are not required to be AD. An oral BFS container, which is prefilled, can therefore reduce the risk of reuse that might occur with a separate oral delivery device.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Oral vaccine delivery devices are not required to be sterile.

	Better *than the comparator*

Indicator: Likelihood of needle stick injury

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 8.

Likelihood of needle stick injury	Parameters to measure against a comparator	Score	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Neutral	BFS packaging does not impact the number of sharps used, as sharps are not required for the comparator.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Neutral	BFS packaging does not impact the use of sharps for preparing and administering the vaccine.
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	For oral vaccines, AD features are not required for delivery. A BFS dropper/dispenser is not AD, and neither is the comparator.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	No sharps are involved for BFS dropper/dispensers similar to the comparator.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	BFS packaging has no impact on the risk of injury after administration.

	***No difference** to the comparator*

3.4 Economic costs criteria

Indicator: Total economic cost of storage and transportation of commodities per dose[c]

*Legend: Dark Green: **Considerably better** than the comparator: Reduces the volume per dose for applicable parameters; Green: **Better** than the comparator: Reduces the volume per dose for either of the applicable parameter, and there is no difference for the other; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the volume for one of the parameter, and increases the volume for the other parameter compared to the comparator; Red: **Worse** than the comparator: Increases the volume per dose for either of the applicable parameters, and there is no difference for the other; Dark Red: **Considerably worse** than the comparator: Increases the volume per dose for both parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 9.

Total economic cost of storage and transportation of commodities per dose	Parameters to measure against a comparator	Score	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Better	BFS containers (dependent on design) have the potential to be smaller in volume than single dose glass vials. For example, the volume per dose for the MMD Rotarix vaccine is 11.8 cm^3 per dose while for an oral vaccine in a single dose glass vial the volume per dose is 16.8 cm^3 (2,7).
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Better	For oral delivery, a BFS container eliminates the need for a separate delivery device and hence no volume is stored outside the cold chain.

	Considerably better *than the comparator*

[c] The assessment of the indicator is volume-related and builds upon PATH's VTIA analysis. A directional estimation is made at this stage, and a better evaluation will be done in Phase II with more antigen-specific data.

Indicator: Total economic cost of the time spent by staff per dose

*Legend: Dark Green: **Considerably better** than the comparator: Reduces time for all applicable parameters; Green: **Better** than the comparator: Reduces time for either, and there is no difference for the other one; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the time for one of the parameters, and increases the time for the other parameter; Red: **Worse** than the comparator: Increases the time for either of the applicable parameters; and there is no difference for the other one; Dark Red: **Considerably worse** than the comparator: Increases time for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 10.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Better	For oral vaccines, delivery time can be reduced when using a BFS container as there is no need to draw a dose into a separate delivery device (1).
	[d]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	The innovation does not have any attributes that impact the time for staff involved in stock management.

	***Better** than the comparator*

[d] This parameter only applies to barcodes and RFID to capture the benefits for stock management processes, not based on the number of components, but the specific features of the innovation.

Indicator: Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)

*Legend: White: **Neutral**: NO there are no one-time/upfront or recurrent costs and this is not different than the comparator; Red: **Worse** than the comparator: YES, there are one-time/upfront or recurrent costs.*

Table 11.

Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	There are no upfront or recurrent costs associated with the use of this innovation, other than (minimal) training costs which would be needed with the introduction of any innovation. However, we are not including training costs as part of the assessment in this phase.

	No difference *to the comparator*

3.5 Secondary criteria on potential breadth of innovation use

Indicator: Applicability of innovation to one or several types of vaccines

Table 12.

Applicability of innovation to one or several types of vaccines • *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	The innovation could be used with liquid vaccines that are administered orally. It is possible that vaccines that are currently given as IN sprays could be given as IN drops using a BFS dropper (8). Compatibility of a vaccine with the BFS filling process and material would have to be assessed on a case-by-case basis. Examples of VIPS priority antigens that would be well-suited for a BFS dispenser/dropper include OPV and liquid rotavirus (2). In 2019, GSK licensed a new presentation of Rotarix vaccine in a strip of 5 single-dose BFS squeeze tubes which stacks to minimize the cold chain footprint.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination • *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	BFS is a primary container technology and is not expected to impact the ability to combine vaccines relative to standard glass vial packaging.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	BFS primary containers have been used commercially at large scale in both high-income and LMIC settings for packaging a variety of pharmaceuticals. They have also been introduced in LMICs for vaccine diluents. A small-scale in country feasibility study was conducted by PATH on prototype oral BFS primary containers in Ghana and India (1). A preliminary cost of goods sold and total cost of delivery study has been conducted by PATH (4). Definitive laboratory testing on vaccine compatibility/stability with BFS has been conducted by vaccine manufacturers.
Inconsistency of results	Not enough studies have been conducted to assess consistency of results.
Indirectness of comparison • *Indicate the setting in which the study was conducted (low, middle or high income setting);* • *Comment if the data is on non-vaccine application of the innovation*	Oral BFS vaccine container usability and cost studies conducted by PATH were in LMIC immunization delivery settings.

Overall assessment:	*Moderate*	

4.2 List of technical experts, manufacturers and/or technology developers interviewed for inputs:

Table 15.

Expert/type	Organisation/contact details	Notes
N/A	N/A	No interviews conducted.

4.3 List of technical experts, manufacturers and/or technology developers that have reviewed and provided feedback/input to the technical notes:

Table 16.

Reviewers	Organisation/contact details	Notes
Courtney Jarrahian	PATH cjarrahian@path.org	Developed TN
PATH Medical Device and Health Technology Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Reviewed TN
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed TN

4.4 References:

Peer-reviewed publications of primary data, systematic reviews, other reports:

1. PATH. *Delivery Systems for Oral Rotavirus Vaccine: An Evaluation of Usability, Acceptability, and Operational Fit in India and Ghana*. Seattle: PATH; 2016.

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